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Posted Date: 1 May 2024

doi: [10.20944/preprints202405.0058.v1](https://doi.org/10.20944/preprints202405.0058.v1)

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Article

Risk Factors Associated with Lost to Follow Up Tuberculosis Treatment in the Sanatorium Hospital of Luanda, Angola

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Abstract: Background: Tuberculosis (TB) continues to be a serious public health threat that affects the most vulnerable population. Patients who are LTFU after TB diagnosis still represent one of the biggest challenges to TB control. **Method:** In this prospective observational study, we aimed to identify and analyse the risk factors associated with LTFU among TB patients who started first-line TB treatment in the Sanatorium Hospital in Luanda. **Result:** A total of 113 patients with TB were included between August 2018 and September 2019. Seventy-six (67.3%) patients were cured, 27 (23.9%) were LTFU, 5 (4.4%) died, 4 (3.5%) were transferred and 1 (0.9%) presented a treatment failure. After excluding those dead, transferred or who failed to treatment, we observed that severe TB at the time of diagnosis (OR 9.24, 95% CI 2.18-39.04) and food insecurity were significantly associated with LTFU (OR 5.96, 95% CI 1.66-21.41). **Conclusion:** The findings of our study are of enormous value to understand the reasons for the LTFU of patients with TB and can guide policies and facilitate designing measures to allow better adherence, and therefore, greater treatment success.

Keywords: Tuberculosis; Loss to follow-up; Food insecurity

1. Introduction

Tuberculosis (TB) continues to be a public health concern worldwide representing the second cause of death from a single infectious agent after COVID-19. In 2021, approximately 10 million new TB cases were reported worldwide with 1.5 million deaths. In 2014 the end TB strategy was launched with specific targets for the reduction of TB incidence, death and catastrophic costs.[1]

A lost to follow-up (LTFU) patient is defined as a TB patient who did not start treatment or whose treatment was interrupted for at least two consecutive months [2]. Patients with TB who are LTFU are at a greater risk of death and drug resistance development [3,4] and can become sources of infection in the community leading to community outbreaks [5-7]. Moreover, LTFU patients increase the cost of TB treatment [8]. Hence, LTFU must be one of the primary concerns in combating TB.

Many factors have been related to LTFU of TB patients. Male sex, smokers and patients with alcohol abuse have been consistently found to be most commonly LTFU [9]. Besides the individual and behavioural characteristics, social determinants as lack of familial support and long distance to the health centres clearly limits adherence to treatment [10]. Similarly, lack of basic education has been found to be related to treatment abandonment. It has been thought that illiterate people may have more difficulty understanding clinical recommendations, and more easily fall into

misunderstandings [10]. In addition, it has been hypothesized that most TB patients with little or no knowledge of the infection and the disease live in precontemplation which difficult adherence to treatment and follow-up [4]. Besides, adverse drug events and length of the treatment facilitates the lack of therapy adherence, especially in those patients with multidrug resistant TB (MDR-TB)[3].

Angola is one of the 30 countries with the greatest TB and MDR-TB burden worldwide [1]. To date, there is little data about the risk factors for LTFU among TB patients in the country [11]. Therefore, the aim of this study was to identify and analyse the risk factors associated with LTFU of TB treatment in patients treated for TB in Sanatorium Hospital in Luanda.

2. Methods

This is an observational prospective study including patients with pulmonary and extrapulmonary TB who started first-line TB treatment in the Sanatorium Hospital in Luanda between August 1st 2018 and September, 30th 2019. Patients older than 15 years old who started first-line TB treatment (microbiologically confirmed by Xpert MTB/Rif, acid-fast bacilli (AFB) smear or empirically treated) and who signed the written informed consent were included. Multidrug resistant TB (MDR-TB) patients and those who were admitted in coma were excluded.

Basal data was recorded and follow-up was done until the end of treatment or until they were LTFU. Sociodemographic variables included gender, age, place of residence (urban or suburban), distance to the health centre (< 10 miles (near) compared to > 10 miles (far)), homeownership, transportation fees to the hospital (<600 vs ≥ 600 Kwanzas), level of education (basic, medium and university studies) ethnicity (Bakongo, Umbundu, Kimbundu and other), religion (Christianity, Islam, Hindu and no religion), current employment, monthly income (low salary < 80000 kwanzas and medium salary > 80000 Kwanzas) and family support during disease. Moreover, to explore if religion played a role in the outcome of the treatment, participants were asked if they believed that God was a TB healer, if they knew anyone who had stopped treatment due to religious reasons or if they knew someone that was cured by a prayer. We also explored the participants' knowledge about TB including 7 basic questions about the causative agent, transmission, clinical manifestations, diagnosis, treatment and prevention. Patients were considered to have knowledge about TB if they correctly answered at least 2 questions. Medical history included smoking habit, alcohol consumption, familiar and personal history of TB, comorbidities, TB symptoms (fever, cough, weight loss, night sweats, asthenia, thoracic pain, dyspnoea, haemoptysis) and site of TB (pulmonary vs extrapulmonary). Severe TB was defined as a patient who presented an oxygen saturation below 90% and/or massive haemoptysis.

Regarding diagnosis of TB, we collected information about AFB sputum smear (negative, scanty (1–9 AFB in 100 fields), 1+ (10–99 AFB in 100 fields), 2+ (1–10 AFB per field), and 3+ (more than 10 AFB per field), Xpert MTB/RIF qualitative and semiquantitative results and chest X-ray results (presence of cavities). Tuberculosis treatment information was also recorded and adverse events were classified as skin toxicity, arthritis, gastrointestinal symptoms and hepatic toxicity. The outcome of the treatment was defined as per the 2013 WHO recommendations including cured and treatment complete (treatment success), LTFU, died, transferred and failure [12].

2.1. Data Analysis

The database was designed in Microsoft Excel, and it was transferred to the SPSS software for Windows (Version 19.0; SPSS Inc, Chicago, IL, USA) for the statistical analysis. Qualitative variables were expressed as absolute numbers and percentages, while quantitative ones were expressed through means and standard deviations (SD) or median and interquartile range (IQR) depending on the distribution. The χ^2 test or Fisher exact test, when appropriate, was used to compare the distribution of categorical variables, and the t-Student or Mann-Whitney test for continuous variables. Results were considered statistically significant if the 2-tailed P value was < 0.05. For the univariate and multivariate analysis, we excluded those patients who died, were transferred or had a treatment failure. The variable TB outcome was banded in two groups (cured and LTFU) and considered as the dependent variable. Variables with a p-value < 0.20 in the univariate analysis or those considered to be clinically important were included in the multivariate logistic regression analysis.

2.2. Ethical Considerations

The study was designed, implemented and reported in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and was approved by the ethics committee of the Ministry of health of Angola (MINSA) N° 06/2018.

3. Results

3.1. Sociodemographic Data and TB Knowledge

A total of 113 patients with TB were included. Sixty-seven (59.3%) were males and the median (IQR) age was 30 [22–44] years old. Sociodemographic data is presented in table 1.

Table 1. Sociodemographic characteristics.

	N = 113
Sex (male)	67 (59.3%)
Age (years)	30 [22–44]
Location	
Urban	23 (20.4%)
Suburban	90 (79.6%)
House ownership	27 (23.9%)
Transportation fee	
<600 kwanzas	94 (83.2%)
≥600 kwanzas	19 (16.8%)
Education	
Basic incomplete	39 (34.5%)
Basic complete	21 (18.6%)
Medium incomplete	27 (23.9%)
Medium complete	19 (16.8%)
University	7 (6.2%)
Ethnicity	
Bakongo	23 (20.4%)
Umbundu	33 (29.2%)
Kimbundu	51 (45.1%)
Other	6 (5.3%)
Religion	
Christianity	107 (94.7%)
Islam	1 (0.9%)
Hindu	1 (0.9%)
No religion	4 (3.5%)
Employment	46 (40.7%)
Salary (n=46)	
Low (<80,000 kwanzas)	40 (86.9%)
Medium (≥80,000 Kwanzas)	6 (13%)
Smoking	23 (20.4%)
Alcohol abuse	39 (34.5%)

Comorbidities

Asthma	7 (6.2%)
Diabetes	13 (11.5%)
HIV	22 (19.5%)
Chronic heart failure	8 (7.1%)
Hypertension	34 (30.1%)
Malaria infection	39 (34.5%)

Number of meals per day

Less than three meals	50 (44.2%)
Three meals	63 (55.8%)

Values are expressed as number and percentage or median [IQR] otherwise specified. HIV: Human Immunodeficiency Virus.

The majority of respondents (107, 94.7%) stated that God could heal TB; 16 (14.2%) reported knowing someone who had been cured by a prayer, and 8 (7.1%) reported knowing someone who had stopped treatment for religious reasons. Overall, 46 (40.7%) patients knew at least two of the seven questions related to TB.

3.2. Clinical Symptoms and Diagnosis

One-hundred (88.5%) patients were diagnosed with TB for the first time. The most common TB symptoms were weight loss in 104 (92.0%), fever 103 (91.2%) and cough 103 (91.2%). Ninety-eight (86.7%) cases were diagnosed with pulmonary TB and 27 (23.9%) presented a severe TB at the moment of diagnosis. Ninety out of the ninety-eight pulmonary TB (91.8%) were able to provide a sputum sample and 62 (68.8%) had a positive sputum smear. Molecular testing by Xpert MTB/rif was performed in 22 patients and all of them had a positive result for TB. Chest X-ray was done in 72 (63.7%) patients and 47 (65.3%) of them presented lung cavitation. Clinical symptoms and diagnosis data is presented in table 2.

Table 2. Clinical presentation, diagnosis, follow-up and outcomes.

	N=113
History of TB in the family	26 (23%)
TB patient	
New case	100 (88.5%)
Previously treated	13 (11.5%)
Symptoms and signs	
Fever	103 (91.2%)
Cough	103 (91.2%)
Weight loss	104 (92%)
Night sweats	78 (69%)
Asthenia	73 (64.6%)
Thoracic pain	49 (43.4%)
Dyspnea	37 (32.7%)
Hemoptysis	17 (15%)
Adenopathies	7 (6.2%)
Ascites	2 (1.8%)
Column deformation	9 (8%)

AFB sputum smear	90 (79.6%)
Positive	62 (68.9%)
Negative	28 (31.1%)
Xpert MTB/RIF	22 (19.5%)
Positive	22 (100%)
Chest X-ray	72 (63.7%)
Cavitation	47 (65.3%)
Severe TB	27 (23.9%)
Type of TB	
Pulmonary	98 (86.7%)
Extrapulmonary	13 (11.5%)
Pulmonary and extrapulmonary	2 (1.8%)
	23 (20.4%)
Adverse events (nº of patients presenting at least one)	23 (20.4%)
Skin toxicity	5 (21.7%)
Arthritis	1 (4.3%)
Gastrointestinal symptoms	14 (60.9%)
Liver toxicity	3 (13%)
Treatment outcome	
Cured	76 (67.3%)
Lost to follow-up	27 (23.9%)
Died	5 (4.4%)
Transferred	4 (3.5%)
Failure	1 (0.9%)

Values are expressed as number and percentage otherwise specified. TB: Tuberculosis.

3.3. Treatment and Outcomes

All patients (113, 100%) were treated with the standard first-line four-drug regimen for TB. Twenty-three (20.4%) patients presented at least one adverse event with the most frequent being gastrointestinal symptoms (14, 60.9%) and skin toxicity (5, 21.7%). Regarding treatment outcomes, 76 (67.3%) patients were cured, 27 (23.9%) were LTFU, 5 (4.4%) died, 4 (3.5%) were transferred and 1 (0.9%) had a treatment failure.

3.4. Variables associated with LTFU

In the univariate analysis, we observed that men (74.1% vs 25.9%, p=0.03), those who usually ate less than three meals per day (65.8% vs. 33.3%, p=0.002) and those who presented a severe TB at the time of diagnosis (37.0% vs. 15.8%, p=0.021) were more frequently LTFU. No other sociodemographic, lifestyle and health factors were significantly related to TB outcome. Regarding TB beliefs and knowledge, we observed that people who were cured believed in God as a TB healer in a greater proportion than those who were LTFU (98.7% vs. 88.9%, p=0.024). No significant association was found between having knowledge about TB and treatment outcome (32.9% vs. 22.2%, p=0.299). This information is summarized in Table 3.

Table 3. Univariate analysis of risk factors and LTFU

N = 103	Cured (76, 73.8%)	LTFU (27, 26.2%)	P value
Sex (male)	38 (50%)	20 (74.1%)	0.03

Age (years)	28 [21–41]	35 [25–46]	0.22
Area of residence			
Urban	14 (18.4%)	6 (22.2%)	0.22
Suburban	62 (81.6%)	21 (77.8%)	
House ownership			
18 (23.7%)	6 (22.2%)	0.87	
Family support			
64 (84.2%)	19 (70.4%)	0.87	
Transportation			
fee	64 (84.2%)	22 (81.5%)	0.74
≤ 600 kwanzas	12 (15.8%)	5 (18.5%)	
> 600 kwanzas			
Education			
Basic incomplete	26 (34.2%)	10 (37.1%)	
Basic complete	15 (19.7%)	6 (22.2%)	
Medium incomplete	17 (22.4%)	6 (22.2%)	0.95
Medium complete	12 (15.8%)	4 (14.8%)	
University	6 (7.9%)	1 (3.7%)	
Ethnicity			
Bakongo	17 (22.4%)	5 (18.5%)	
Umbundu	23 (30.3%)	8 (29.6%)	0.93
Kimbundu	32 (42.1%)	13 (48.1%)	
Other	4 (5.3%)	1 (3.7%)	
Religion			
Christianity	75 (98.7%)	24 (88.9%)	
Islam	0	1 (3.7%)	0.09
Hindu	0	1 (3.7%)	
No religion	1 (1.3%)	1 (3.7%)	
Employment			
29 (38.2%)	10 (37%)	0.91	
Salary			
No salary	47 (61.8%)	17 (63%)	
Low salary	24 (31.6%)	9 (33.3%)	0.85
Medium salary	5 (6.6%)	1 (3.7%)	
Smoking			
12 (15.8%)	7 (25.9%)	0.24	
Alcohol abuse			
21 (27.6%)	11 (40.7%)	0.21	
Comorbidities			
Asthma	4 (5.3%)	2 (7.4%)	0.68
Diabetes	6 (7.9%)	3 (11.1%)	0.61
HIV	15 (19.7%)	7 (25.9%)	0.50
Chronic heart failure	3 (3.9%)	2 (7.4%)	0.47
	20 (26.3%)	9 (33.3%)	0.48

Hypertension	26 (34.2%)	8 (29.6%)	0.66
Malaria			
Number of meals			
per day	26 (34.2%)	18 (66.6%)	0.002
Less than three	50 (65.8%)	9 (33.3%)	
Three meals			
Religious beliefs			
God can heal TB	75 (98.7%)	24 (88.9%)	0.02
Someone stops treatment for religion	5 (6.6%)	2 (7.4%)	0.08
for	13 (17.1%)	3 (11.1%)	0.46
Cured by a prayer			
TB knowledge	25 (32.9%)	6 (22.2%)	0.29
Familiar history	18 (23.7%)	8 (29.6%)	0.54
Symptoms and signs			
Fever	69 (90.8%)	24 (88.9%)	0.77
Cough	67 (88.2%)	26 (96.3%)	0.22
Weight loss	7 (9.2%)	2 (7.4%)	0.77
Night sweats	48 (63.2%)	21 (27.6%)	0.16
Asthenia	46 (60.5%)	19 (70.4%)	0.36
Thoracic pain	36 (47.4%)	7 (25.9%)	0.05
Dyspnea	27 (35.5%)	6 (22.2%)	0.20
Hemoptysis	12 (15.8%)	2 (7.4%)	0.27
Adenopathies	5 (6.6%)	1 (3.7%)	0.58
Ascites	2 (2.6%)	0	0.39
Column deformity	7 (9.2%)	2 (7.4%)	0.77
AFB sputum smear			
Positive	41 (53.9%)	15 (55.6%)	
Negative	21 (27.6%)	6 (22.2%)	0.82
Not performed	14 (18.4%)	6 (22.2%)	
AFB sputum quantification			
0	35 (46.1%)	12 (44.4%)	
1+	12 (15.9%)	6 (7.9%)	0.89
2+	20 (26.3%)	6 (7.9%)	
3+	9 (11.8%)	3 (11.1%)	

Chest X-ray			
Cavitation	33 (50%)	11 (16.7%)	0.81
Severe TB	12 (15.8%)	10 (37%)	0.02
Type of TB			
Pulmonary	66 (86.8%)	25 (92.6%)	
Extrapulmonary	8 (10.5%)	2 (7.4%)	0.98
Pulmonary and extrapulmonary	2 (2.6%)	0	
Type of TB patient			
New case	7 (9.2%)	5 (18.5%)	
Previously treated			
Adverse events	15 (19.7%)	6 (7.9%)	0.78
Type of adverse events			
Skin toxicity	1 (1.3%)	0	0.12
Arthritis	10 (13.2%)	3 (3.9%)	
Gastrointestinal toxicity	0	2 (2.6%)	
Liver toxicity			

Values are expressed as number and percentage or median [IQR] otherwise specified. HIV: Human Immunodeficiency Virus, AFB: Acid Fast Bacilli, TB: Tuberculosis.

In the multivariate analysis, we only observed that those patients with a severe TB at the moment of diagnosis and those who usually ate less than 3 meals per day were significantly associated with LTFU ((OR 9.24, 95% CI 2.18-39.04, p=0.006) and (OR 5.96, 95% CI 1.66-21.41, p=0.006) respectively) (See Table 4).

Table 4. Multivariate analysis of risk factors and LTFU.

	OR	95% CI	P value
Gender (male)	3.32	0.9-12.1	0.091
Eat less than 3 times a day	5.96	1.66-21.41	0.006
Belief in God as healer of TB	0.24	0.02-70.01	0.251
Previously treated patients	0.54	0.09-3.12	0.493
Severe TB	9.24	2.18-39.04	0.002
Knowledge about TB	0.25	0.04-1.34	0.107

4. Discussion

In this prospective observational study evaluating factors associated with LTFU during TB treatment in Luanda we described a high proportion of patients who were LTFU (23.9%). We noted that those patients with severe TB at presentation and those who ate less than 3 times a day were more likely to drop out of treatment and become LTFU. In our study, treatment success was lower than expected compared with other experiences in the sub-Saharan African region. Success rates from other countries range between 82% to 92% [13]-[15]. Our LTFU figures are also lower than those

reported by the WHO Global report 2022 for people treated with first line anti-TB drugs (86%)[1]. Undoubtedly, this low treatment success is related to the high percentage of loss to follow-up and dropout observed in our study.

When we analysed the risk factors related to LTFU we revealed that being male was significantly associated with the risk of discontinuing treatment although the statistical significance was lost in the multivariate analysis. Despite that, being male has consistently been found as a risk factor for LTFU. As there is no biological reason that can be linked to the higher dropout rate among men, the most common explanations have been related to the social and cultural sphere. As an example, Santos et al. observed that, in the Angolan society as well as other cultures in the region, there is a higher social pressure on man to be the economic driver to support the family. This fact could justify that men could be less constant for medical controls and treatment adherence [11]. Another explanation is that men usually consume more alcohol or other illicit drugs than women, habits widely described as risk factors for therapeutic non-compliance [16].

As Angola is a country with a strong Christian faith, we wanted to investigate if religion played a role during TB treatment and its outcome. In this regard we observed that believing in God as a TB healer was significantly associated with treatment success ($p= 0.024$) although these association was lost in the multivariate analysis. It has been already described that many individuals in Angola continue to believe that Gods and other supernatural entities have a role in their physical and mental health [17]. The majority of respondents (93.4%) believed that praying to God to cure TB would be successful. According to Perdigao et al, the majority of Christians agreed with the idea that God can cure TB [18]. In nations where religious views are highly valued, the cooperation of community and religious leaders is vital for TB control efforts. This permits more effective and culturally appropriate outreach to at-risk populations [17].

On the other hand, we have observed that severe TB at the moment of diagnosis was associated with a higher risk of LTFU in the multivariate analysis. One of the most plausible explanations for this finding is that, when patients are seriously ill or do not improve, their relatives or the patients themselves prefer to go to traditional medicine and then get LTFU [19]. In addition, there may be family conflicts after the death of a patient in the hospital, and families may prefer to have the patient die at home [20]. Moreover, patients with a more severe disease tend to be admitted for longer periods of time, thus consuming more economic resources, making it easier to incur catastrophic costs and, therefore, making it more difficult for patients to continue outpatient follow-up once they are discharged [21].

We noted that those patients who could not guarantee 3 daily meals per day were more often LTFU. We believe that, in this case, the number of meals per day is a proxy of poverty. There is a reciprocal relationship between poverty and tuberculosis. Poverty may be related to poor sanitary conditions that increase susceptibility to tuberculosis and the disease limits work and livelihood opportunities, thus forming a vicious circle that tends to worsen the severity and negative impact of the disease. Tuberculosis is related to unfavourable socioeconomic conditions, which usually worsen when a member of the household is ill. Catastrophic costs associated with TB are present in more than 40% of families affected by TB, and frequently affect the most vulnerable population [22]. Regardless of medicines for TB being free in most settings, including Angola, there are some expenses that the patients have to incur, such as consultation fees, laboratory tests, and other indirect costs such as transportation and family accommodation. Moreover, in Angola, main meals during hospital admission are not paid by the health system and have to be afforded by patients. In the same way, in Angola, most patients do not have health insurance and have no income while they are sick and unable to work. This condition portrays that patients have to distinguish and prioritise between the treatment of the TB and food respectively [23]. Unfortunately, we did not find any other relation between LTFU and other surrogate markers of poverty (e.g., salary).

There are several limitations in our study. First, despite having been designed as a prospective cohort of patients treated with anti-TB drugs, the number of patients included during the study period was lower than expected. Several changes in the direction of the Luanda Sanatorium Hospital and the difficulty of being in the country to enrol patients in the study, has had a significant impact on the final number of included patients. A higher number of patients could have resulted in more robust data. Second, some of the patients included in the study were diagnosed clinically, without microbiological confirmation for TB. It is possible that some of the patients included in our study did

not really have TB, but rather another respiratory infection, a fact that could have influenced the treatment outcome. Third, the interviews were all conducted at the Hospital Sanatorium de Luanda, so patients who had dropped out and then never returned to consultations were not included. The perspective of people in the community who do not return to hospital can give another view of the reasons for LTFU.

In conclusion, our findings show a high proportion of LTFU patients during TB treatment in Luanda, and that a severe TB presentation at the moment of diagnosis was significantly associated with LTFU TB treatment. Eating less than 3 times per day was significantly associated with LTFU TB treatment. These findings reinforce the fact that the fight against poverty is clearly necessary to end TB.

Author Contributions: Domingos Vita (Conceptualization, methodology, investigation, writing original draft), Maria Luisa Aznar (methodology, data analysis, supervision, writing review-editing), Joan Martínez-Campreciós (data curation, writing-review and editing), Debora Cristina Maindo Sebastiao Kansietoko (investigation, writing-review and editing), Israel Molina (methodology, supervision, writing-review and editing).

Funding: This research received no external funding.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors thank the health authorities in Angola and all the participate in this study.

Conflicts of Interest: The authors declare no conflict of interest.

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